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TELEFAX TRANSMITTAL

TO: Examiner Monshipouri

FIRM: U.S. Patent and Trademark Office

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FROM: Micheline Gravelle

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COMMENTS:

Re: U.S. Patent Application No. 09/926,036
National Phase Entry Application of PCT/CA00/00165
International Filing Date: February 18, 2000

As requested by Examiner Monshipouri, please find enclosed a copy of the International Preliminary Examination Report issued for the above-referenced patent PCT application.

Regards,

M. Gravelle

Micheline Gravelle
Registration No. 40,261

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BERESKIN & PARR
40 King Street West, 40th Floor
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.06.2001
Applicant's or agent's file reference: 3244-37	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00165	18/02/2000	19/02/1999

Applicant
McMASTER UNIVERSITY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Emslander, S Tel.+49 89 2399-8718

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3244-37		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00165	18/02/2000	19/02/1999
International Patent Classification (IPC) or national classification and IPC C12N9/00		
Applicant McMASTER UNIVERSITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/09/2000	19.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vollbach, S Telephone No. +49 89 2399 8715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00165

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-55 as originally filed

Claims, No.:

1-21 with telefax of 20/03/2001

Drawings, sheets:

1/18-18/18 as originally filed

Sequence listing part of the description, pages:

1-20, filed with the letter of 01.05.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00165

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,4-6,8-21
	No:	Claims	2,3,7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,4-6,8-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present set of claims comprises, on the one hand, product claims 1-5,7-9 and 17 and, on the other hand, method claims 6,10-16,18-21.

As far as the product claims are concerned, none of them is novel and/or inventive in view of the fact that an "Ste20-like kinase protein" (SMAK) which has 97.4% identity with the protein of Fig. 2 has already been disclosed in the art (see D1:DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 17 January 1998 (1998-01-17), XP002144032 HINXTON, GB). In particular, claim 1 is novel, but cannot be considered to involve an inventive step. Claims 2, 3 and 7 embrace the disclosure of D1 and are thus inadmissible under Article 33(2) PCT. Insofar as the remaining product claims are concerned an inventive step cannot be recognized in view of D1, because the provision of probes, a vector, a host cell and antibodies of a known protein in general is not considered inventive (Article 33(3) PCT). This also applies to the method of claim 6.

As far as the remaining method claims are concerned, they relate to the use of the "SMAK" or parts thereof for the modulation of apoptosis and/ or cell proliferation.

Most of said claims merely characterise the agent to be used by the arbitrary designation SMAK and, therefore, are unclear (Article 6 PCT). The designation in fact has no limiting character on the scope and covers structurally unrelated proteins which share the same vague defined function.

Therefore, all of these claims lack an inventive step according to Article 33(3) PCT, i.e. claims 10,12-16,18-21.

On the other hand, the exact function of the specific protein was not disclosed in D1 and a correlation thereof to apoptosis was not indicated.

This does not apply to fragments and derivatives. Therefore also claims 11, if novel, lacks an inventive step.

Therefore, for those claims which (a) contain a suitably characterised product (i.e. characterised by its sequence), and (b) contain a reference to apoptosis novelty and inventive step could be acknowledged.

On the other hand, merely a general reference to "modulating cell proliferation" (see claims 13-16) cannot establish an inventive activity over D1 in combination with the general

common knowledge relating to related kinases since all of them are involved in one or the other manner in cell proliferation (see several of the documents cited in the search report). Therefore the use of the protein for this general purpose (which is not even a directed purpose but merely a "modulating" effect) must be regarded as being obvious.

The same applies for the general methods for identification (claims 20) of the general assay (claim 21).

2. For the assessment of the present claims 10-16 and 18-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

see item V. of the present report.

WE CLAIM:

1. A purified and isolated nucleic acid molecule, comprising (i) a nucleic acid sequence encoding a SMAK protein having the amino acid sequence as shown in Figure 2; and, (ii) nucleic acid sequences complementary to (i).

2. A purified and isolated nucleic acid molecule as claimed in claim 1, comprising

(i) a nucleic acid sequence encoding a SMAK protein having the nucleic acid sequence as shown in Figure 1, wherein T can also be U;

(ii) a nucleic acid sequence complementary to (i);

(iii) a nucleic acid molecule differing from any of the nucleic acids of (i) and (ii) in codon sequences due to the degeneracy of the genetic code.

3. A purified and isolated nucleic acid molecule comprising a sequence which hybridizes to the nucleic acid molecule as claimed in claim 1 or 2.

4. A recombinant expression vector adapted for transformation of a host cell comprising a nucleic acid molecule as claimed in any one of claims 1 to 3 and one or more transcription and translation elements operatively linked to the nucleic acid molecule.

5. A host cell containing a recombinant expression vector as claimed in claim 4.

6. A method for preparing a SMAK protein comprising (a) transferring a recombinant expression vector as claimed in claim 4 into a host cell; (b) selecting a transformed host cell from untransformed host cells; (c) culturing the selected transformed host cell under conditions which allow expression of the SMAK protein; and (d) isolating the SMAK protein.

7. A purified and isolated SMAK protein comprising the amino acid sequence as shown in Figure 2, or a fragment, analog or derivative thereof.

8. Antibodies having specificity against an epitope of the SMAK protein as claimed in claim 7.

9. A nucleotide probe comprising a sequence encoding at least 6 continuous amino acids from the SMAK protein shown in Figure 2.

10. A method of modulating apoptosis comprising administering an effective amount of a SMAK protein or a nucleic acid encoding a SMAK protein to a cell or animal in need thereof.

11. A method according to claim 10 wherein the SMAK protein has the amino acid sequence shown in Figure 2 or a fragment analog or derivative thereof.

12. A method according to claim 10 wherein the nucleic acid molecule encoding the SMAK protein is according to any one of claims 1 to 3.

13. A method of modulating cell proliferation comprising administering to the cell an effective amount of an agent which inhibits the expression or activity of SMAK protein.

14. A method according to claim 13 wherein the agent is an antibody to a SMAK protein.

15. A method according to claim 13 wherein the agent is an antisense molecule that is complimentary to a nucleic acid molecule encoding a SMAK protein.

16. A method according to any one of claims 13 to 15 wherein the cell is in an animal.

17. A purified and isolated polypeptide which has an amino acid sequence of an ATH domain of SMAK protein.

18. A method of modulating apoptosis comprising administering to a cell an effective amount of a polypeptide which has an amino acid sequence of an ATH domain of a SMAK protein.

19. A method according to claim 18 wherein the cell is in an animal.

20. A method for identifying a substance which is capable of binding to a purified and isolated SMAK protein as claimed in claim 7, comprising reacting the protein with at least one substance which potentially can bind with the protein under conditions which permit the formation of complexes between the substance and the protein, and assaying for complexes, for free substance, for non-complexed protein, or for activation of the protein.

21. A method for assaying a medium for the presence of an agonist or antagonist of the interaction of a purified and isolated a SMAK protein as claimed in claim 7 and a substance which binds to the protein which comprises reacting the protein with a substance which is capable of binding to the protein and a suspected agonist or antagonist substance under conditions which permit the formation of complexes between the substance and the protein, and assaying for complexes, for free substance, for non-complexed protein, or for activation of the protein.